Sedation and analgesia practices in neonatal intensive care units (EUROPAIN): results from a prospective cohort study

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Summary

Background Neonates who are in pain or are stressed during care in the intensive care unit (ICU) are often given sedation or analgesia. We investigated the current use of sedation or analgesia in neonatal ICUs (NICUs) in European countries.

Methods EUROPAIN (EUROpean Pain Audit In Neonates) was a prospective cohort study of the management of sedation and analgesia in patients in NICUs. All neonates admitted to NICUs during 1 month were included in this study. Data on demographics, methods of respiration, use of continuous or intermittent sedation, analgesia, or neuromuscular blockers, pain assessments, and drug withdrawal syndromes were gathered during the first 28 days of admission to NICUs. Multivariable linear regression models and propensity scores were used to assess the association between duration of tracheal ventilation (TV) and exposure to opioids, sedatives-hypnotics, or general anaesthetics in neonates (O-SH-GA). This study is registered with ClinicalTrials.gov, number NCT01694745.

Findings From Oct 1, 2012, to June 30, 2013, 6680 neonates were enrolled in 243 NICUs in 18 European countries. Mean gestational age of these neonates was 35·0 weeks (SD 4·6) and birthweight was 2384 g (1007). 2142 (32%) neonates were given TV, 1496 (22%) non-invasive ventilation (NIV), and 3042 (46%) were kept on spontaneous ventilation (SV). 1746 (82%), 266 (18%), and 282 (9%) neonates in the TV, NIV, and SV groups, respectively, were given sedation or analgesia as a continuous infusion, intermittent doses, or both (p<0·0001). In the participating NICUs, the median use of sedation or analgesia was 89·3% (70·0–100) for neonates in the TV group. Opioids were given to 1764 (26%) of 6680 neonates and to 1589 (74%) of 2142 neonates in the TV group. Midazolam was given to 576 (9%) of 6680 neonates and 536 (25%) neonates of 2142 neonates in the TV group. 542 (25%) neonates in the TV group were given neuromuscular blockers, which were administered as continuous infusions to 146 (7%) of these neonates. Pain assessments were recorded in 1250 (58%) of 2138, 672 (45%) of 1493, and 916 (30%) of 3017 neonates in the TV, NIV, and SV groups, respectively (p<0·0001). In the univariate analysis, neonates given O-SH-GA in the TV group needed a longer duration of TV than did those who were not given O-SH-GA (mean 136·2 h [SD 173·1] *vs* 39·8 h [94·7] h; p<0·0001). Multivariable and propensity score analyses confirmed this association (p<0·0001).

Interpretation Wide variations in sedation and analgesia practices occur between NICUs and countries. Widespread use of O-SH-GA in intubated neonates might prolong their need for mechanical ventilation, but further research is needed to investigate the therapeutic and adverse effects of O-SH-GA in neonates, and to develop new and safe approaches for sedation and analgesia.

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Introduction

According to compelling evidence, all newborn babies, including those born preterm, respond to pain.[1,2] Recurring pain in neonates leads to poor cognition[3] and motor function,[4] impaired brain development,[5,6] and altered pain responses.[7] Since care in the neonatal intensive care unit (NICU) involves invasive and non-invasive procedures, mechanical ventilation, and medical or surgical disorders that can cause pain or stress, widespread practices include the administration of sedation and analgesia to patients in the NICU.[8] Recent concerns about the neurotoxic effects of analgesics (including opioids), sedatives, and anaesthetics on the developing brain[9] have triggered a debate about their potential neuroprotective and neurotoxic effects in newborn babies.[10] Very little is known, however, about international sedation and analgesia practices at the bedside. Research into the comparative effectiveness of these practices and the factors associated with them will enable the definition of best practices and future clinical trials.

We aimed to describe the current use of sedation, analgesia, and neuromuscular blockers at the bedside in NICUs in European countries and to describe the factors associated with sedation or analgesia use.

Methods

Study design and participants

EUROPAIN (EUROpean Pain Audit In Neonates) was a prospective cohort study of the management of pain and

Research in context

Evidence before this study

We did a MEDLINE search using the words "pain", "newborn", "sedation", and "analgesia" in different combinations without any date restrictions, and a cross-reference search of the articles we found yielded only three studies that briefly included, among other objectives, the assessment of general sedation or analgesia practices in the neonatal intensive care unit (NICU). Two were declarative national surveys and one was a cross-sectional survey. In Swedish NICUs, pharmacological analgesia was used during mechanical ventilation but no information was reported about the type or frequency of drugs used; 33 (37%) of 90 Italian NICUs reported routine use of opioid drugs for mechanical ventilation. The results of a survey done in 1993–94 in 14 Canadian NICUs showed that 51 (21%) of 239 neonates received analgesia or anaesthesia, or both, during a 1 week study period. Most of the other excluded epidemiological studies assessed procedural pain management or particular situations (postoperative, mechanical ventilation during chronic lung disease, or necrotising enterocolitis) in the NICU. For the clinical effects of the use of opioid drugs, sedatives-hypnotics, or general anaesthetics in neonates who were tracheally ventilated, a search of the Cochrane database yielded two systematic reviews on the use of opioid drugs and the use of midazolam. One systematic review was of ten studies that reported the duration of tracheal ventilation during treatment with opioid drugs; a meta-analysis of six studies showed no significant effect of opioid administration on the duration of tracheal ventilation. The other systematic review was of three studies on intravenous infusion of midazolam for sedation of infants in the NICU to ascertain whether midazolam was an effective sedative and to assess clinically significant short-term and long-term adverse effects. A significantly longer stay in NICU was noted in the midazolam group than in the placebo group. No data for the duration of tracheal ventilation were reported.

Added value of this study

To our knowledge, this is the first prospective, multicentre, international study reporting 24 h bedside practices of sedation and analgesia in European NICUs. Our study cohort was representative of NICU populations in Europe and other developed countries with the participation of 18 countries, standardisation of data gathering, and more than 90% inclusion rates in 16 of 18 countries. The inclusion of 2142 neonates who were tracheally ventilated and the wide range of practices enabled a robust identification of factors associated with the use of sedation or analgesia in these infants and a detailed analysis of the association between the use of opioids, sedatives-hypnotics, or general anaesthetics and the duration of tracheal ventilation. Unlike the results of previous studies, treatment with opioids, sedatives-hypnotics, or general anaesthetics was associated with prolonged ventilation in neonates who were tracheally ventilated. We noted that 34% of NICU admissions and 82% of neonates who were tracheally ventilated received some sedation or analgesia with wide variations in practices between different NICUs and different countries. 74% of neonates who were tracheally ventilated received opioids and a quarter received midazolam.

Implications of all available evidence

The wide variations in sedation and analgesia practices between different NICUs and different countries in this study and the association of the use of opioids, sedatives-hypnotics, or general anaesthetics with increased durations of tracheal ventilation emphasise the need to develop international guidelines for judicious use of sedation or analgesia in the NICU, to investigate the therapeutic and adverse effects of these drugs in neonates, and to develop new safe approaches for sedation or analgesia in neonates in intensive care.

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See **Online** for appendix

stress with sedation and analgesia in patients in the NICU, without interfering with routine clinical practices. The background, objectives, and methods of the study in different languages, with detailed videos on how to complete online questionnaires, and all documents and daily progress reports were accessible through the survey website. All material and documents used or obtained for this study, such as protocols in English and other national languages, posters, PowerPoint presentations for local teams, announcements, and ethics committee approvals, were available online. Website links connected authorised users to a secure server hosting the application Voozanoo (version 3) for data entry into standardised questionnaires in the national language.

By contacting national neonatal societies and existing networks, we identified a volunteer neonatologist or neonatal nurse in each country (Austria, Belgium, Cyprus, Estonia, Finland, France, Germany, Greece, Italy, Lithuania, Malta, the Netherlands, Norway, Poland, Portugal, Spain, Sweden, and the UK) to be the national principal investigator. The national principal investigator for each country invited the chiefs of all existing NICUs to participate in this study. The letter of invitation was standardised and written in English for all countries and had a web-link to the online study questionnaires. The national principal investigators added a personal explanation in their national language to this letter. Level 3 units were globally defined as units that are able to provide care for critically ill neonates of all gestational ages and weights and that provide mechanical ventilation support for as long as needed. Level 3 NICUs that initiated and did the complete period of tracheal ventilation (TV) were eligible, whereas NICUs transferring ventilated newborn babies to other units were not eligible. To avoid distortion of the appraisal of the real management of neonates in intensive care units (ICUs), paediatric intensive care units (PICUs) that cared for neonates also participated in the study. All centres that agreed to

For the **EUROPAIN survey** see www.europainsurvey.eu

participate identified a nurse and a physician coordinator, and a data quality manager. Nurse and physician coordinators in each unit provided information to the principal investigators about general statistics and local sedation and analgesia protocols for neonates. The national principal investigator provided data to the principal investigators about national guidelines for the management of pain in neonates.

Study protocols and data gathering were first approved in France by the regulatory organisations for the Protection of Human Subjects and data, and health research data management, and then approved by similar committees in each country and, if necessary, at each participating site. Information sheets were given to parents to explain that the gathered data would be anonymous and they could opt out of their child's participation at any time.

Data gathering

All neonates up to 44 weeks of post-conception age who were admitted to the NICU during enrolment were eligible for inclusion in the study; neonates already in the NICU at the start of enrolment were not included in the study. We gathered data prospectively for each neonate during the first 28 days of stay in the hospital, or until death, discharge, or transfer to another hospital on the demographics, methods of respiration, use of continuous or intermittent (bolus) sedation, analgesia, or neuromuscular blockers, pain assessments with any validated scale (a list of scales was available on the data gathering form and NICUs could add any other scale they used), and specific practices to treat or prevent drug withdrawal syndromes. Data were gathered for the types of ventilation used or study medications given irrespective of the reasons for their use in the NICU. We did not gather data on medications given before admission to the NICU. We did not obtain data on daily sedation interruptions or vacations, use of sedation scales, or the type or number of invasive or non-invasive procedures. The exact durations of continuous infusion of sedatives or analgesics were registered; for bolus administration, we recorded the number of daily doses. Neonates were classified as being in the sedation or analgesia group if they received at least one dose of medication. NICUs recruited patients over 1 month, which was judged to be sufficient to study the practices of all rotating personnel while minimising temporal changes in clinical practices. Not all the NICUs included patients during the same period. Recruitment periods were determined by the completion of regulatory compliances of NICUs, preferences, and capability of the monitoring team in Paris, France, to follow the inclusion of patients. This monitoring team aimed at having no more than 40 NICUs recruiting patients at the same time because the team followed and checked inclusion of every patient. Data were gathered on standardised paper questionnaires and then entered online, or were entered directly online. Each NICU also kept a log book of all neonates admitted during the study.

A centralised monitoring team in Paris monitored the completeness of data entered into the study database and identified potential errors by checking the coherence of entered data. Missing or potentially incongruous data were reported to unit coordinators and double checked locally. After the inclusion of all the patients, the monitoring team randomly selected 10% of patients (a minimum of five patients) and the local data quality manager double checked all the data for these patients. If 1% or more errors were detected, the data for another 10% of patients were double checked; if error rates of 1% persisted, all data entries from that NICU were double checked.

Statistical analysis

We anticipated the participation of at least 15 countries and planned to make comparisons between all countries. We used a χ^2 power analysis to calculate the sample size. We expected small differences in sedation or analgesia practices between countries and thus used an effect size (W) of 0·1 for calculations. By use of NCSS-PASS (version 2008), a sample size of 2303 neonates would achieve 90% power to detect an effect size of 0·1 with 14 degrees of freedom (15 centres), using a χ^2 test with an α of 0·05 (see appendix for further details).

We used SPSS (version 17.0) for the analysis of descriptive data and Stata (version 13.0) for multivariable models and propensity score procedures. To elucidate factors associated with sedation or analgesia use, clinical factors correlated with the use of sedation or analgesia ($p<0·2$) in the univariate analysis were included in logistic regression models, with stepwise backward elimination of non-significant covariates. Independent variables were country, sex, gestational age, type of respiratory support, severity of illness (Clinical Risk Index for Babies [CRIB] score: consists of six items measured in the first 12 h after birth and ranges from 0 to 23, with higher scores indicating higher clinical risk), age at admission, intrauterine growth retardation, respiratory distress syndrome, 1 min and 5 min Apgar scores, intubation at NICU admission, and assessment with a pain scale. Because data were clustered, p values and 95% CIs were adjusted with a robust sandwich estimator. Results of regression analyses are presented as odds ratio (OR) with two-sided 95% CIs. An internal validation of the logistic model was done with a bootstrap approach with 1000 samples.

We assessed the association between exposure to opioids, sedatives-hypnotics, or general anaesthetics (O-SH-GA) and duration of tracheal ventilation in infants because of concern about the prolongation of invasive ventilation. All covariates associated ($p<0·20$) with duration of tracheal ventilation in univariate analyses were included in multivariable linear regression models

	Total (n=6680)	Tracheal ventilation (n=2142)	Non-invasive ventilation (n=1496)	Spontaneous ventilation (n=3042)	p value*
Gestational age (weeks)					
Mean (SD)	35·0 (4·6)	32·7 (5·2)	33·8 (3·8)	37·3 (3·1)	<0·0001
Median (IQR)	35·6 (32·0–39·0)	32·1 (28·1–37·4)	33·6 (31·0–36·6)	37·9 (35·0–39·9)	<0·0001
24–29	1049 (16%)	779 (36%)	214 (14%)	56 (2%)	<0·0001†
30–32	1015 (15%)	360 (17%)	454 (30%)	201 (7%)	
33–36	1864 (28%)	389 (18%)	486 (32%)	989 (33%)	
37–42	2750 (41%)	613 (29%)	342 (23%)	1795 (59%)	
Birthweight (g)					
Mean (SD)	2384 (1007)	1948 (1035)	2132 (891)	2816 (855)	<0·0001
Median (IQR)	2370 (1570–3170)	1740 (1000–2800)	1970 (1440–2720)	2870 (2140–3445)	<0·0001
Sex, male	3775 (57%)	1260 (59%)	842 (56%)	1673 (55%)	0·10
Born in same hospital as NICU	5367 (80%)	1460 (68%)	1307 (87%)	2600 (85%)	<0·0001
Type of delivery					<0·0001
Vaginal	3074 (46%)	879 (41%)	571 (38%)	1624 (53%)	
Caesarean	3586 (54%)	1249 (59%)	923 (62%)	1414 (47%)	
Age at admission (h)					
Mean (SD)	65·2 (244·3)	84·1 (294·0)	47·5 (224·2)	60·6 (212·3)	<0·0001
Median (IQR)	1·0 (0·3–12·1)	0·8 (0·3–8·3)	0·5 (0·2–1·7)	3·0 (0·4–26·8)	<0·0001
CRIB score					
Mean (SD)	1·4 (2·5)	3·3 (3·5)	0·8 (1·5)	0·4 (1·0)	<0·0001
Median (IQR)	0 (0–2)	2 (1–5)	0 (0–1)	0 (0–0)	<0·0001
Apgar score at 5 min					
Mean (SD)	8·4 (1·9)	7·4 (2·4)	8·5 (1·4)	9·0 (1·3)	<0·0001
Median (IQR)	9 (8–10)	8 (6–9)	9 (8–10)	9 (9–10)	<0·0001
Already intubated at admission	1376 (21%)‡	1376 (64%)	NA	NA	NA
Died during study	211 (3%)	201 (9%)	3 (<1%)	7 (<1%)	<0·0001
Hospital admission (days)§					
Mean (SD)	11·9 (9·7)	15·7 (10·2)	14·2 (9·9)	8·0 (7·4)	<0·0001
Median (IQR)	8 (3–20)	14 (6–28)	11 (5–26)	5 (3–11)	<0·0001
Duration of ventilation (h)					
Tracheal ventilation¶					
Mean (SD)	NA	115 (164)	NA	NA	NA
Median (IQR)	NA	49 (15–130)	NA	NA	NA
Non-invasive ventilation¶					
Mean (SD)	NA	178 (197)	92 (148)	NA	NA
Median (IQR)	NA	84 (24–294)	34 (13–97)	NA	NA
Spontaneous ventilation¶					
Mean (SD)	NA	207 (192)	249 (213)	169 (179)	NA
Median (IQR)	NA	139 (45–340)	173 (55–437)	103 (39–233)	NA
Sedatives or analgesics					
Method of administration					
Any form‖	2294 (34%)	1746 (82%)	266 (18%)	282 (9%)	<0·0001**
Continuous only	309 (5%)	294 (14%)	5 (<1%)	10 (<1%)	
Bolus only	937 (14%)	452 (21%)	247 (17%)	238 (8%)	
Continuous and bolus	1048 (16%)	1000 (47%)	14 (1%)	34 (1%)	
Type††					
Opioid analgesics	1764 (26%)‡‡	1589 (74%)	87 (6%)	88 (3%)	<0·0001
Sedatives-hypnotics	786 (12%)	690 (32%)	43 (3%)	53 (2%)	<0·0001
Midazolam	576 (9%)	536 (25%)	16 (1%)	24 (1%)	
Barbiturates	96 (1%)	69 (3%)	8 (1%)	19 (1%)	

(Table 1 continues on next page)

	Total (n=6680)	Tracheal ventilation (n=2142)	Non-invasive ventilation (n=1496)	Spontaneous ventilation (n=3042)	p value*
(Continued from previous page)					
Other	195 (3%)	157 (7%)	20 (1%)	18 (1%)	
General anaesthetics	199 (3%)	178 (8%)	13 (<1%)	8 (<1%)	<0·0001
Ketamine	136 (2%)	120 (6%)	9 (<1%)	7 (<1%)	
Propofol	65 (1%)	59 (3%)	5 (<1%)	1 (<1%)	
Inhalational anaesthetics	3 (<1%)	3 (<1%)	0 (0%)	0 (0%)	
Paracetamol	904 (14%)	530 (25%)	172 (11%)	202 (7%)	<0·0001
Ibuprofen	16 (<1%)	14 (1%)	1 (<1%)	1 (<1%)	<0·0001
Local anaesthetics	26 (<1%)	21 (1%)	2 (<1%)	3 (<1%)	<0·0001
Other drugs	16 (<1%)	11 (1%)	0 (0%)	5 (<1%)	0·0038
Neuromuscular blockers	542 (8%)	542 (25%)	0 (0%)	0 (0%)	<0·0001
Pain assessment with a scale§§	2838 (42%)	1250 (58%)	672 (45%)	916 (30%)	<0·0001
Withdrawal syndrome diagnosed	94 (1%)	69 (3%)	4 (<1%)	21 (1%)	<0·0001

Some variables had missing values. NICU=neonatal intensive care unit. NA=not applicable. CRIB=Clinical Risk Index for Babies. *Comparisons of the three types of ventilation were done with χ^2 (Fisher's exact test when required), ANOVA, or Kruskal-Wallis test. †χ^2 for distributions in all strata of gestational ages within the three ventilation groups. ‡26 infants were intubated immediately on arrival in the NICU and thus were included in this group. §Data gathering was stopped on day 28 of hospital stay; 1043 (16%) of 6679 neonates were hospitalised for longer than 28 days. ¶For the tracheal ventilation group, time on non-invasive ventilation or spontaneous ventilation refers to non-invasive ventilation or spontaneous ventilation before tracheal intubation or after extubation; and for the non-invasive ventilation group, time on spontaneous ventilation refers to the periods of spontaneous ventilation before or after non-invasive ventilation use. ||Continuous or bolus, or both. **χ^2 for comparisons of use of any form of sedation analgesia in the three ventilation groups. ††Some neonates were given more than one type of analgesic or sedative. ‡‡Of 1764 neonates, 1707 (97%) were given one or more of the following drugs: morphine (n=1016), fentanyl (n=694), or sufentanil (n=227). §§Information was available for 2138 neonates in the tracheal ventilation group, 1493 in the non-invasive ventilation group, and 3017 in the spontaneous ventilation group.

Table 1: **Baseline characteristics of 6680 neonates and use of sedation and analgesia by ventilation group in the NICUs**

to assess this association. Because infants were not randomly assigned to receive O-SH-GA, we used propensity scores to reduce the effect of treatment-selection bias and potential confounders in the study. The propensity score for an individual is the probability of being treated conditionally based on the individual's covariate values.[11] We calculated the propensity score on the basis of the covariates used in the logistic regression model predicting the use of O-SH-GA. Infants treated and not treated with these drugs but with a similar propensity for treatment with O-SH-GA were matched. The matching was done, after the random ordering of infants, using the psmatch2 algorithm[12] in Stata (version 13.0) with one-to-one nearest neighbour matching without replacement and with maximum calliper distance of 0·125 times the propensity score SD. The covariate imbalance and its correction between the groups treated and not treated with O-SH-GA were measured as the absolute standardised differences for the comparison of the groups. Standardised differences of up to 10% were deemed inconsequential.[13] Using matched pairs, we compared the duration of TV in infants treated or not treated with O-SH-GA. In all the neonates in the TV group, use of two other techniques based on the propensity score, stratification, and regression adjustment, confirmed the analyses done in matched pairs.[11] Stratification based on propensity score quintiles divided the TV group into five strata. Within each stratum, infants treated or not treated with O-SH-GA were compared. Previous research showed that this technique removes up to 90% bias caused by confounding variables.[11] To further adjust for confounders, two multivariable linear regression models predicting duration of TV were constructed, one including only the propensity score and O-SH-GA treatment status as independent variables and another including these variables plus all variables significantly associated with the duration of TV in univariate analyses. Because the rate of mortality can have an effect on the duration of TV, we used the number of ventilator-free days as a secondary endpoint to estimate the effect of the use of O-SH-GA. This outcome is largely used in reports about ICUs.[14] Ventilator-free days were defined as the number of calendar days from the time of tracheal extubation to day 28 after NICU admission. If a neonate was reintubated and subsequently extubated before day 28, ventilator-free days were counted from the end of the last period of tracheal intubation. If a neonate was receiving TV on day 28 or died before day 28, ventilator-free days were zero.[15] For neonates discharged before day 28 of admission, ventilator-free days were zero if the neonate was still intubated at discharge (transfer) and ventilator-free days were counted from the time of tracheal extubation to day 28 after NICU admission if the neonate was already extubated at discharge. Ventilator-free days were compared with the paired-sample Wilcoxon rank test. Two-tailed p values of 0·05 or less were deemed significant.

The study is registered with ClinicalTrials.gov, number NCT01694745.

	Total (n=2064)	Tracheal ventilation (n=1139)	Non-invasive ventilation (n=668)	Spontaneous ventilation (n=257)	p value*
Gestational age (weeks)					
Mean (SD)	29·4 (2·5)	28·4 (2·5)	30·4 (1·9)	30·9 (2·1)	<0·0001
Median (IQR)	29·9 (27·4–31·6)	28·4 (26·4–30·4)	30·9 (29·4–32·0)	31·6 (30·0–32·3)	<0·0001
Birthweight (g)					
Mean (SD)	1269 (436)	1131 (417)	1419 (397)	1490 (394)	<0·0001
Median (IQR)	1230 (920–1580)	1045 (801–1395)	1411 (1116–1718)	1500 (1255–1755)	<0·0001
Sex, male	1154 (56%)	674 (59%)	352 (53%)	128 (50%)	0·009
Born in same hospital as NICU	1681 (81%)	909 (80%)	590 (88%)	182 (71%)	<0·0001
Type of delivery					0·015
Vaginal	708 (34%)	401 (35%)	204 (31%)	103 (40%)	
Caesarean	1352 (66%)	735 (65%)	463 (69%)	154 (60%)	
Age at admission (h)					
Mean (SD)	125·6 (395·1)	110·9 (373·1)	79·2 (312·4)	311·5 (586·4)	<0·0001
Median (IQR)	0·5 (0·3–1·8)	0·5 (0·3–2·0)	0·4 (0·2–0·9)	0·8 (0·3–273·5)	<0·0001
CRIB score					
Mean (SD)	2·5 (3·3)	3·8 (3·7)	1·1 (1·7)	1·0 (1·8)	<0·0001
Median (IQR)	1 (0–4)	2 (1–6)	1 (0–1)	0 (0–1)	<0·0001
Apgar score at 5 min					
Mean (SD)	8·0 (1·9)	7·4 (2·1)	8·6 (1·3)	9·0 (1·2)	<0·0001
Median (IQR)	8 (7–9)	8 (6–9)	9 (8–9)	9 (9–10)	<0·0001
Already intubated at admission	811 (39%)†	811 (71%)	NA	NA	NA
Died during study	139 (7%)	139 (12%)	0 (0%)	0 (0%)	<0·0001
Hospital admission (days)‡					
Mean (SD)	19·4 (9·8)	19·8 (9·9)	19·4 (9·6)	17·3 (9·4)	0·001
Median (IQR)	25 (10–28)	28 (10–28)	25 (9–28)	18 (8–28)	<0·0001
Duration of ventilation (h)					
Tracheal ventilation§					
Mean (SD)	NA	147 (194)	NA	NA	NA
Median (IQR)	NA	58 (18–182)	NA	NA	NA
Non-invasive ventilation§					
Mean (SD)	NA	243 (208)	155 (192)	NA	NA
Median (IQR)	NA	181 (53–429)	70 (25–188)	NA	NA
Spontaneous ventilation§					
Mean (SD)	NA	269 (215)	341 (227)	394 (227)	NA
Median (IQR)	NA	221 (67–472)	359 (110–565)	417 (171–649)	NA
Sedatives or analgesics					
Method of administration					
Any form¶	1031 (50%)	881 (77%)	124 (19%)	26 (10%)	<0·0001‖
Continuous only	155 (8%)	154 (14%)	1 (<1%)	0 (0%)	
Bolus only	420 (20%)	279 (24%)	119 (18%)	22 (9%)	
Continuous and bolus	456 (22%)	448 (39%)	4 (1%)	4 (2%)	
Type**					
Opioid analgesics	851 (41%)††	796 (70%)	49 (7%)	6 (2%)	<0·0001
Sedatives-hypnotics	272 (13%)	255 (22%)	15 (2%)	2 (1%)	<0·0001
Midazolam	197 (10%)	190 (17%)	5 (1%)	2 (1%)	
Barbiturates	16 (1%)	12 (1%)	4 (1%)	0 (0%)	
Other	63 (3%)	58 (5%)	5 (1%)	0 (0%)	
General anaesthetics	82 (4%)	72 (6%)	10 (1%)	0 (0%)	<0·0001
Ketamine	42 (2%)	35 (3%)	7 (1%)	0 (0%)	
Propofol	42 (2%)	38 (3%)	4 (1%)	0 (0%)	
Inhalational anaesthetics	2 (<1%)	2 (<1%)	0 (0%)	0 (0%)	

(Table 2 continues on next page)

	Total (n=2064)	Tracheal ventilation (n=1139)	Non-invasive ventilation (n=668)	Spontaneous ventilation (n=257)	p value*
(Continued from previous page)					
Paracetamol	326 (16%)	229 (20%)	73 (11%)	24 (9%)	<0·0001
Ibuprofen	15 (1%)	14 (1%)	1 (<1%)	0 (0%)	0·0123
Local anaesthetics	8 (<1%)	7 (1%)	0 (0%)	1 (<1%)	0·13
Other drugs	2 (<1%)	2 (<1%)	0 (0%)	0 (0%)	0·64
Neuromuscular blockers	259 (13%)	259 (23%)	0 (0%)	0 (0%)	<0·0001
Pain assessment with a scale‡‡	1136 (55%)	682 (60%)	342 (51%)	112 (44%)	<0·0001
Withdrawal syndrome diagnosed	15 (1%)	13 (1%)	2 (<1%)	0 (0%)	0·49

Some variables had some missing values. NICU=neonatal intensive care unit. NA=not applicable. CRIB=Clinical Risk Index for Babies. *Comparisons of the three types of ventilation were with χ^2 (Fisher's exact test when required), ANOVA, or Kruskal-Wallis test. †16 infants were intubated immediately on arrival in the unit and thus were included in this group. ‡Data gathering was stopped on day 28 of hospital stay; 848 (41%) of 2064 neonates were hospitalised for longer than 28 days. §For the tracheal ventilation group, time on non-invasive ventilation or spontaneous ventilation refers to non-invasive ventilation or spontaneous ventilation before tracheal intubation or after extubation; and for the non-invasive ventilation group, time on spontaneous ventilation refers to the periods of spontaneous ventilation before or after non-invasive ventilation. ¶Continuous or bolus, or both. ||χ^2 for comparison of methods of administration among the three ventilation groups. **Some neonates were given more than one type of analgesic or sedative. ††Of 851 neonates, 821 (96%) were given one or more of the following drugs: morphine (n=473), fentanyl (n=344), or sufentanil (n=104). ‡‡Information was available for 1135 neonates in the tracheal ventilation group, 665 in the non-invasive ventilation group, and 256 in the spontaneous ventilation group.

Table 2: **Baseline characteristics of 2064 neonates younger than 33 weeks and use of sedation and analgesia by ventilation group in the NICUs**

Role of the funding source

The funder of the study had no role in the design of the study, data gathering, analysis, or interpretation, writing of the report, or in the decision to submit the report for publication. The corresponding author had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analyses, and had final responsibility for the decision to submit for publication.

Results

From Oct 1, 2012, to June 30, 2013, 243 NICUs in 18 European countries enrolled 6680 neonates (appendix). The appendix shows, for each country, how representative participating NICUs were of all eligible NICUs. Six countries (33%) had national guidelines and 182 NICUs (75%) reported local protocols for neonatal sedation or analgesia. The mean gestational age of the neonates was 35·0 weeks (SD 4·6) and the birthweight was 2384 g (1007) (table 1). The mean period of participation in the study was 11·9 calendar days (9·7; table 1) and the neonates were observed for a total of 79 185 patient days.

Patients were classified into three groups depending on the highest level of ventilation needed during the study: TV (n=2142), non-invasive ventilation (NIV; n=1496), and spontaneous ventilation (SV; n=3042). During the study, 99 (5%) of 2142 neonates in the TV group needed surgery (different from the invasive procedures undertaken at the bedside), which was performed by a consultant specialist. Neonates in the TV group had lower gestational age, birthweight, rates of birth in the study hospital, and Apgar scores, and higher age at admission and disease severity scores (CRIB) than did those in the NIV and SV groups (table 1). In the TV group, 64% of neonates of all gestational ages and 71% of those younger than 33 weeks were already intubated at NICU admission (tables 1 and 2).

Of the 6680 neonates enrolled, 2294 (34%) were administered, at least once, sedation or analgesia by continuous infusion or intermittent (bolus) doses or both: 82% in the TV group, 18% in the NIV group, and 9% in the SV group (p<0·0001; table 1). The median use of sedation or analgesia by the 243 NICUs for all neonates and for neonates in the TV group were 33·3% (IQR 18·5–56·5) and 89·3% (70·0–100), respectively.

Opioids included mainly morphine (given to 923 [43%] of 2142, 37 [2%] of 1496, and 56 [2%] of 3042 neonates in the TV, NIV, and SV groups, respectively), fentanyl (629 [29%], 41 [3%], and 24 [1%]), and sufentanil (220 [10%], two [<1%], and five [<1%]); sedatives-hypnotics included mainly midazolam (536 [25%], 16 [1%], and 24 [1%]), chloral hydrate (83 [4%], 17 [1%], and 13 [<1%]), and phenobarbital (54 [3%], seven [<1%], and 19 [1%]); general anaesthetics included mainly ketamine (120 [6%], nine [1%], and seven [<1%]) and propofol (59 [3%], five [<1%], and one [<1%]; propofol was always administered as a bolus). Opioids were the most commonly administered medication to neonates followed by sedative-hypnotics and general anaesthetics (table 1). Figure 1 shows the frequencies and methods of administration of all sedation and analgesia drugs, opioids, and sedatives-hypnotics in the TV group by country. It shows that opioids were given to more than 95% of neonates in the TV group in Cyprus, Lithuania, and Malta and to less than 70% in Austria, France, Germany, Greece, Portugal, and Spain. Sedatives-hypnotics were given to more than 50% of infants in the TV group in Austria, Estonia, Germany, and Sweden, and were not given to tracheally ventilated neonates in Cyprus and Malta.

Figure 2 shows the frequencies and methods of administration of commonly used opioids, midazolam,

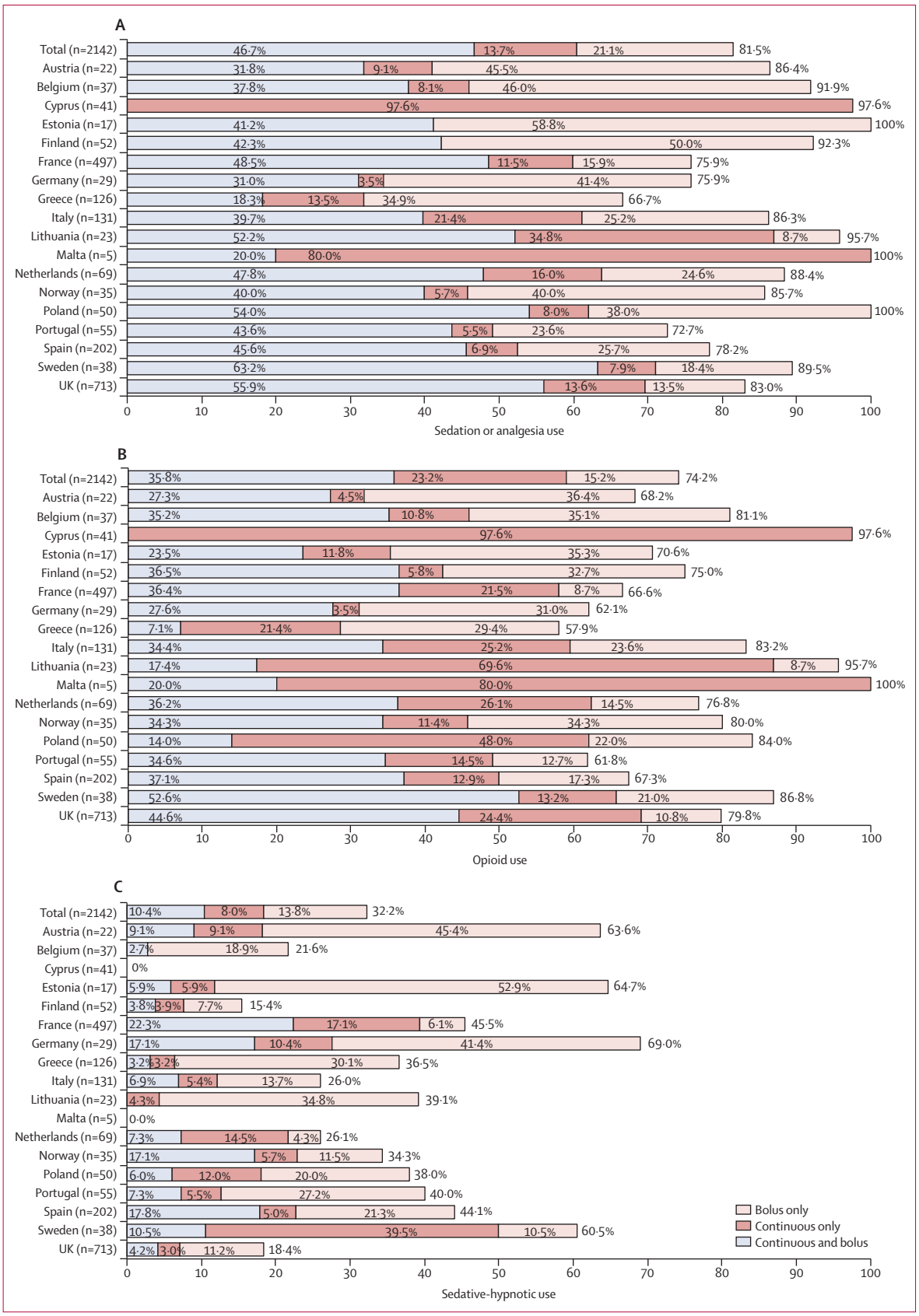

Figure 1: **European and national frequencies of the use of sedation and analgesia (A), opioids (B), and sedatives-hypnotics (C) in 2142 neonates given tracheal ventilation**

propofol, chloral hydrate, ketamine, and paracetamol. In the NIV and SV groups, paracetamol was the most frequently used sedative analgesic in 172 (11%) of 1496 and 202 (7%) of 3042 infants, respectively. All the other drugs were used in less than 3% of infants and were administered mainly as boluses. In the TV group, 542 (25%) of 2142 neonates were given neuromuscular blockers, including suxamethonium (205 [10%]), atracurium (115 [5%]), and pancuronium (82 [4%]). Neuromuscular blockers were given exclusively as boluses to 396 (18%) neonates in the TV group and as continuous infusions to 146 (7%) neonates. The median duration of infusion of neuromuscular blockers was 33·9 h (IQR 13·4–65·9; range 0·2–422·0). In the TV group, neuromuscular blockers were given to 183 (23%) of 779 neonates born at 24–29 weeks gestation, 76 (21%) of 360 neonates of gestational age 30–32 weeks, 95 (24%) of 389 neonates of gestational age 33–36 weeks, and 187 (31%) of 613 neonates of gestational age 37–42 weeks (p=0·0034); data were missing for one neonate in the TV group. All neonates who were given neuromuscular blockers were also given O-SH-GA. Bedside assessments using a pain scale were recorded in 1250 (58%) of 2138, 672 (45%) of 1493, and 916 (30%) of 3017 neonates in the TV, NIV, and SV groups, respectively (p<0·0001; table 1). Of 2838 neonates who had a pain assessment with a scale, the Enfant Douleur Nouveau-Né (EDIN) scale was used in 1200 (42%) neonates, Comfort Behavior in 416 (15%), Neonatal Pain, Agitation and Sedation Scale (N-PASS) in 279 (10%), Comfort Scale in 213 (8%), Premature Infant Pain Profile (PIPP) score in 139 (5%), Neonatal Infant Pain Scale (NIPS) in 113 (4%), Pain Assessment Tool in 101 (4%), Crying, Requires oxygen for saturation of more than 95%, Increased vital signs, Expressions, and Sleepless (CRIES) scale in 45 (2%), and other scales in 636 (22%). Only one scale was used during an assessment; however, some neonates had assessments with different scales at different times. The references for the pain assessment scales are provided in the appendix.

Of 2142 neonates in the TV group, 1674 (78%) were treated with O-SH-GA including 1634 (76%) who were given opioids or midazolam, or both. 1290 (60%) neonates in the TV group were given continuous infusions of O-SH-GA. 451 (21%) neonates of 2142 were given sedation or analgesia solely as boluses, including 382 (18%) who were given O-SH-GA. Only 91 (4%) neonates were given four boluses or more and 28 (1%) were given ten boluses or more. 199 (9%) neonates were given one bolus or two boluses of O-SH-GA only on the day of a tracheal intubation. The reasons for bolus administration were not recorded.

The 2142 neonates in the TV group accounted for 33715 patient-days of observation, including 12638 patient-days with TV and 21077 patient-days

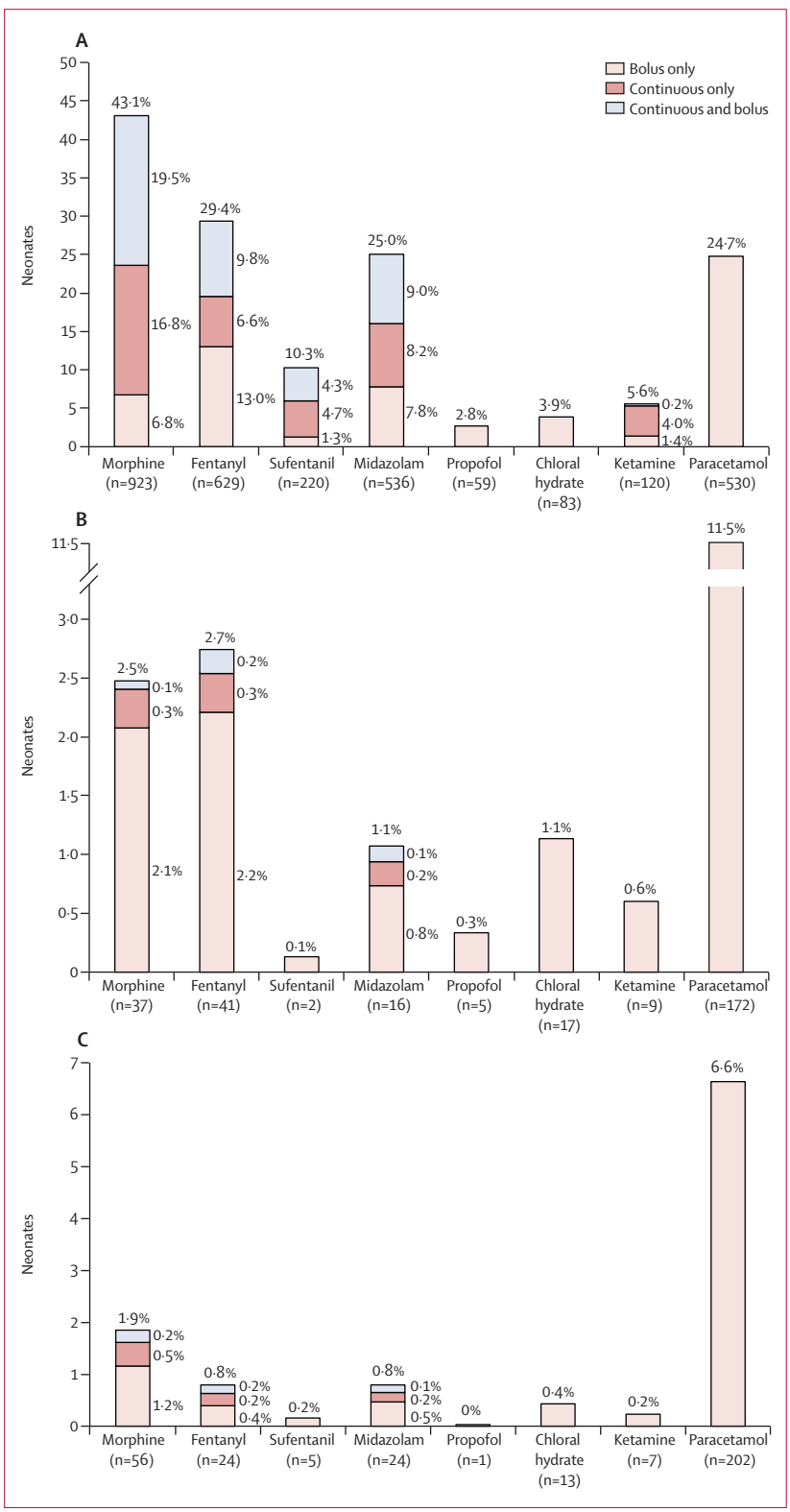

Figure 2: **Frequencies and methods of administration of morphine, fentanyl, sufentanil, midazolam, propofol, chloral hydrate, ketamine, and paracetamol according to type of ventilation**
(A) Tracheal ventilation (n=2142). (B) Non-invasive ventilation (n=1496). (C) Spontaneous ventilation (n=3042). Percentages were calculated with the total number of neonates per ventilation group.

	All neonates (n=6307)					Tracheally ventilated neonates (n=2004)				
	Number	Any sedation or analgesia†		Opioids, sedatives-hypnotics, or general anaesthetics‡		Number	Any sedation or analgesia†		Opioids, sedatives-hypnotics, or general anaesthetics‡	
		Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value		Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Sex										
Male	3563	1·00		1·00		1180	1·00		1·00	
Female	2744	0·86 (0·74–1·00)	0·06	0·94 (0·79–1·12)	0·49	824	0·85 (0·66–1·09)	0·21	0·82 (0·65–1·04)	0·10
Gestational age (weeks)										
37–42	2604	1·00		1·00		574	1·00		1·00	
33–36	1765	0·61 (0·50–0·74)	<0·0001	0·76 (0·60–0·95)	0·019	372	0·58 (0·39–0·87)	0·009	0·75 (0·51–1·09)	0·13
30–32	971	0·60 (0·47–0·76)	<0·0001	0·62 (0·47–0·82)	0·001	343	0·48 (0·32–0·74)	0·001	0·50 (0·34–0·73)	<0·0001
24–29	967	0·47 (0·36–0·61)	<0·0001	0·51 (0·39–0·67)	<0·0001	715	0·59 (0·38–0·90)	0·014	0·65 (0·45–0·95)	0·025
Age at admission (h)										
>168	459	1·00		1·00		172	1·00		1·00	
73–168	245	0·68 (0·44–1·06)	0·09	0·88 (0·52–1·51)	0·66	46	1·04 (0·20–5·51)	0·96	1·42 (0·36–5·59)	0·62
25–72	470	0·64 (0·44–0·94)	0·022	0·85 (0·53–1·38)	0·51	88	0·65 (0·23–1·82)	0·41	0·82 (0·36–1·88)	0·65
7–24	711	0·60 (0·42–0·85)	0·004	0·78 (0·51–1·18)	0·24	213	0·50 (0·20–1·24)	0·14	0·79 (0·39–1·61)	0·52
<7	4422	0·40 (0·30–0·53)	<0·0001	0·39 (0·28–0·54)	<0·0001	1485	0·17 (0·08–0·38)	<0·0001	0·28 (0·16–0·51)	<0·0001
Intrauterine growth retardation										
No	5208	1·00		1·00		1680	1·00		1·00	
Yes	1099	0·83 (0·67–1·03)	0·09	0·90 (0·71–1·16)	0·42	324	0·70 (0·49–0·99)	0·044	0·80 (0·58–1·01)	0·17
Respiratory distress syndrome										
No	4432	1·00		1·00		1029	1·00		1·00	
Yes	1875	0·75 (0·62–0·90)	0·002	1·06 (0·87–1·30)	0·56	975	0·70 (0·52–0·95)	0·021	0·88 (0·67–1·17)	0·38
CRIB score§	6307	1·25 (1·19–1·31)	<0·0001	1·26 (1·21–1·32)	<0·0001	2004	1·33 (1·25–1·42)	<0·0001	1·31 (1·24–1·39)	<0·0001
Apgar at 1 min¶	6307	1·0 (1·0–1·1)	0·15	1·1 (1·0–1·1)	0·009	2004	1·0 (1·0–1·1)	0·07	1·0 (1·0–1·1)	0·25
Already intubated at admission		NA		NA						
No						731	1·00		1·00	
Yes						1273	0·18 (0·13–0·26)	<0·0001	0·21 (0·15–0·28)	<0·0001
Respiratory support										
Spontaneous ventilation	2863	1·00		1·00			NA		NA	
Non-invasive ventilation	1440	2·84 (2·30–3·51)	<0·0001	2·83 (2·13–3·76)	<0·0001					
Tracheal ventilation	2004	43·73 (35·03–54·59)	<0·0001	79·27 (60·55–103·77)	<0·0001					
Pain assessment with a scale										
No	3656	1·00		1·00		848	1·00		1·00	
Yes	2651	1·78 (1·53–2·07)	<0·0001	1·74 (1·47–2·07)	<0·0001	1156	1·82 (1·41–2·35)	<0·0001	1·84 (1·45–2·33)	<0·0001
Model area under the receiver operating characteristic curve‖		0·893 (0·884–0·901)		0·926 (0·919–0·934)			0·797 (0·773–0·821)		0·777 (0·753–0·802)	
Optimism in apparent performance**		0·0001487		0·0000991			0·0003624		0·0001021	
Optimism-corrected area**		0·893 (0·884–0·902)		0·926 (0·919–0·934)			0·797 (0·773–0·821)		0·777 (0·753–0·802)	

Patients with missing data were not included in the logistic regression models. The p values and 95% CIs were adjusted with a robust sandwich estimator. NA=not applicable. CRIB=Clinical Risk Index for Babies. *Analysis adjusted for centres. †Includes opioids, sedatives-hypnotics, general anaesthetics, paracetamol, ibuprofen, local anaesthetics, and other drugs. ‡Opioids, sedatives-hypnotics, or general anaesthetics include all opioids, ketamine, benzodiazepines, propofol, barbiturates, chloral hydrate, and other sedatives; comparison with no analgesia, sedation, or other types of analgesia. §Odds ratio per point increase in CRIB score. ¶Odds ratio per point increase in Apgar score; this score ranges from 0 to 10. ||Area with 95% CI (0·5=no predictive value; 1·0=perfect prediction). **An internal validation of the model was performed using a bootstrap approach (1000 samples).

Table 3: **Logistic regression models of factors associated with the use of any sedation or analgesia and the use of opioids, sedatives-hypnotics, or general anaesthetics in all neonates and tracheally ventilated neonates***

without TV (days before intubation or after extubation). Opioids were used continuously or as bolus, or both, during 7960 (63%) of 12 638 patient-days with TV and only during 807 (4%) of 21 077 patients-days without TV (p<0·0001). Sedatives were used during 2744 patient-days (22%) with TV and 320 patient-days (2%) without TV (p<0·0001); midazolam was used for 2196 patient-days (17%) and 114 patient-days (1%), respectively (p<0·0001).

	Tracheally ventilated neonates (n=2004)						
	Number of neonates	Opioids		Sedatives-hypnotics		General anaesthetics	
		Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Sex							
Male	1180	1·00		1·00		1·00	
Female	824	0·74 (0·60–0·93)	0·008	0·91 (0·73–1·12)	0·36	1·06 (0·75–1·50)	0·74
Gestational age (weeks)							
37–42	574	1·00		1·00		1·00	
33–36	372	0·91 (0·64–1·29)	0·59	0·62 (0·46–0·83)	0·001	0·68 (0·40–1·15)	0·15
30–32	343	0·55 (0·39–0·79)	0·001	0·32 (0·23–0·46)	<0·0001	0·65 (0·37–1·13)	0·13
24–29	715	0·69 (0·49–0·99)	0·041	0·29 (0·21–0·40)	<0·0001	0·87 (0·53–1·44)	0·60
Age at admission (h)							
>168	172	1·00		1·00		1·00	
73–168	46	1·33 (0·39–4·50)	0·64	0·65 (0·33–1·28)	0·21	1·21 (0·46–3·20)	0·70
25–72	88	0·68 (0·32–1·43)	0·30	0·38 (0·22–0·65)	0·0004	0·74 (0·30–1·87)	0·53
7–24	213	0·84 (0·44–1·61)	0·60	0·48 (0·31–0·74)	0·001	0·60 (0·29–1·23)	0·16
<7	1485	0·32 (0·19–0·55)	<0·0001	0·32 (0·23–0·46)	<0·0001	0·43 (0·25–0·74)	0·002
Intrauterine growth retardation							
No	1680	1·00		1·00		1·00	
Yes	324	0·70 (0·52–0·95)	0·021	1·23 (0·94–1·61)	0·14	1·56 (1·03–2·37)	0·035
Respiratory distress syndrome							
No	1029	1·00		1·00		1·00	
Yes	975	0·86 (0·67–1·12)	0·28	0·77 (0·60–0·98)	0·04	0·77 (0·51–1·17)	0·22
CRIB score†	2004	1·31 (1·24–1·37)	<0·0001	1·13 (1·10–1·17)	<0·0001	1·03 (0·98–1·09)	0·22
Apgar at 1 min‡	2004	1·04 (0·99–1·08)	0·09	1·04 (0·99–1·08)	0·09	0·98 (0·91–1·05)	0·60
Already intubated at admission							
No	731	1·00		1·00		1·00	
Yes	1273	0·35 (0·27–0·46)	<0·0001	0·83 (0·66–1·04)	0·11	0·30 (0·20–0·44)	<0·0001
Pain assessment with a scale							
No	848	1·00		1·00		1·00	
Yes	1156	1·73 (1·39–2·16)	<0·0001	1·80 (1·45–2·23)	<0·0001	2·63 (1·76–3·92)	<0·0001
Model area under the receiver operating characteristic curve§		0·753 (0·729–0·777)		0·731 (0·706–0·755)		0·741 (0·701–0·780)	
Optimism in apparent performance¶		–0·0000247		–0·0003018		0·0004471	
Optimism-corrected area¶		0·753 (0·729–0·777)		0·730 (0·706–0·755)		0·741 (0·701–0·781)	

Patients with missing data were not included in the logistic regression models. The p values and 95% CIs were adjusted with a robust sandwich estimator. CRIB=Clinical Risk Index for Babies. *Analysis adjusted for centres. †Odds ratio per point increase in CRIB score. ‡Odds ratio per point increase in Apgar score; this score ranges from 0 to 10. §Area with 95% CI (0·5=no predictive value; 1·0=perfect prediction). ¶An internal validation of the model was done with a bootstrap approach (1000 samples).

Table 4: **Logistic regression models of factors associated with the use of opioids, sedatives-hypnotics, and general anaesthetics in tracheally ventilated neonates***

1640 (77%) of 2142, 99 (7%) of 1496, and 105 (3%) of 3042 neonates were given opioids or benzodiazepines and 641 (39%) of 1636, 30 (31%) of 97, and 43 (42%) of 103 neonates were weaned off these gradually in the TV, NIV, and SV groups, respectively (p=0·22). A drug withdrawal scale was used during the study for 153 (9%) of 1640, 11 (11%) of 99, and 27 (26%) of 105 neonates treated with opioids or benzodiazepines in the TV, NIV, and SV groups, respectively (p<0·0001); of note, 24 (89%) of 27 neonates in the SV group who had an assessment with a drug withdrawal scale were born to mothers who were addicted to drugs. The scales used for the assessment of withdrawal in 191 neonates were the Finnegan scale in 107 (56%) neonates, Lipsitz scale in 33 (17%), Withdrawal Assessment Tool-1 in eight (4%), Opioid and Benzodiazepine Withdrawal Scale in seven (4%), and other scales in 39 (20%) neonates; the references for the drug withdrawal scales are provided in the appendix. Of neonates who were given opioids or benzodiazepines, 69 (4%) of 1640, four (4%) of 99, and 21 (20%) of 105 neonates were diagnosed with a drug withdrawal syndrome, and 111 (7%), nine (9%), and 24 (23%) were treated or given prophylaxis in the TV, NIV, and SV groups, respectively (p<0·0001). The most

	Univariate analysis (n=2142)			Multivariable linear model* (n=2004)		
	Number of neonates	Duration of tracheal ventilation (h; mean, SD)	p value	Number of neonates	β (SD)	p value
Sex			0·17			0·13
Male	1260	118·99 (166·62)		1180	1·00	
Female	880	109·00 (159·87)		824	−9·84 (6·49)	
Gestational age (weeks)			<0·0001			
37–42	613	76·76 (106·77)		574	1·00	
33–36	389	81·10 (115·34)		372	17·50 (9·94)	0·08
30–32	360	60·53 (99·67)		343	18·01 (10·84)	0·10
24–29	779	187·63 (213·62)		715	100·80 (9·76)	<0·0001
Age at admission (h)			0·013			
>168	224	141·75 (178·97)		172	1·00	
73–168	59	143·35 (164·62)		46	19·03 (23·74)	0·42
25–72	99	80·13 (115·31)		88	−11·91 (19·24)	0·54
7–24	231	117·50 (150·35)		213	9·60 (15·19)	0·53
<7	1529	112·02 (166·15)		1485	−11·29 (12·16)	0·35
Born in same hospital as NICU			0·81		..	
No	682	116·37 (150·87)			..	
Yes	1460	114·53 (170·15)			..	
CRIB score	2057	0·307†	<0·0001	2004	6·79 (1·08)	<0·0001
Apgar at 1 min‡	2088	−0·139†	<0·0001	2004	−2·62 (1·26)	0·037
Intrauterine growth retardation			0·001			0·007
No	1785	109·73 (157·70)		1680	1·00	
Yes	351	141·94 (191·04)		324	23·74 (8·79)	
Respiratory distress syndrome			0·001			0·34
No	1125	103·85 (147·60)		1029	1·00	
Yes	1017	127·57 (180·09)		975	7·56 (7·89)	
Already intubated at admission			<0·0001			<0·0001
No	766	78·72 (109·89)		731	1·00	
Yes	1376	135·37 (184·73)		1273	42·22 (7·64)	
Use of opioids, sedatives-hypnotics or general anaesthetics§			<0·0001			<0·0001
No	468	39·79 (94·71)		445	1·00	
Yes	1674	136·17 (173·14)		1559	96·47 (8·36)	
Pain assessment with a scale			0·002			0·0005
No	888	101·95 (159·86)		848	1·00	
Yes	1250	123·85 (166·09)		1156	28·36 (8·11)	

Patients with missing data were not included in the multivariable linear model. The p values and 95% CIs were adjusted with a robust sandwich estimator. CRIB=Clinical Risk Index for Babies. *Also adjusted for countries. †Pearson correlation with duration of tracheal ventilation. ‡Apgar score ranges from 0 to 10. §Opioids, sedatives-hypnotics, or general anaesthetics include all opioids, ketamine, benzodiazepines, propofol, barbiturates, chloral hydrate, and other sedatives.

Table 5: **Univariate analysis and multivariable linear model of factors associated with increased duration of tracheal ventilation**

common medications used to treat or prevent a drug withdrawal syndrome were morphine in 84 (58%), clonidine in 37 (26%), phenobarbital in 14 (10%), methadone in ten (7%), lorazepam in five (3%), diazepam in four (3%), and other drugs in 26 (18%) of 144 neonates.

The use of sedation or analgesia varied from 0% to 100% between NICUs. Bootstrap internal validation of the models indicated very little optimism bias, which is the difference between the model area under the receiver operator curve and the area we get if we sample new values 1000 times (difference <0·0005 for all models; tables 3 and 4). Thus, the optimism-corrected receiver operating characteristic (ROC) curves were almost the same as the original ROC curves (tables 3 and 4). Contributing factors for the increased use of sedation or analgesia in all neonates were ventilation status, increased CRIB scores, and bedside pain assessments, whereas preterm birth and younger age at NICU admission (<72 h) resulted in a decreased use of sedation or analgesia (table 3). In the TV group, use of O-SH-GA

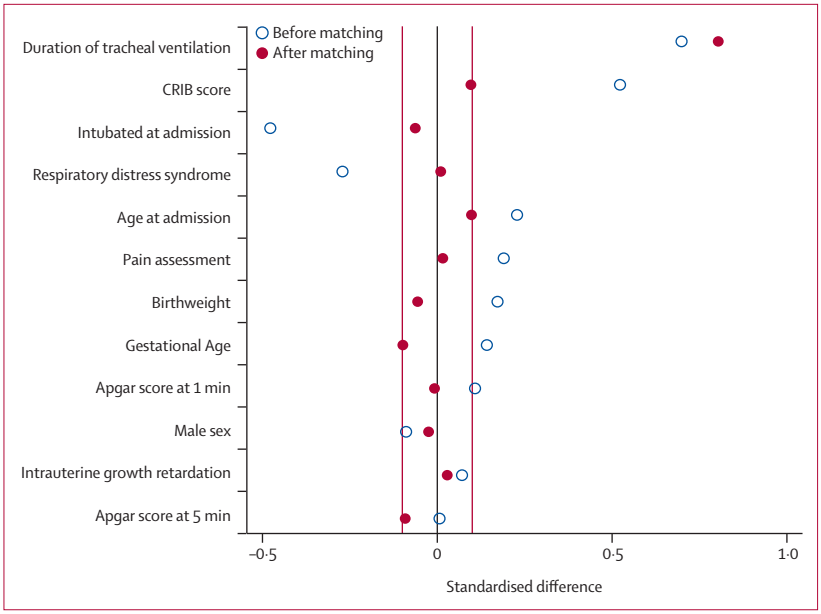

Figure 3: **Reduction by propensity score pair matching of covariate imbalance in infants given opioids, sedatives-hypnotics, or general anaesthetics compared with those who were not**
The sizes of the dots indicate the magnitude of the standardised difference between groups for each variable before and after propensity score matching (appendix). Red lines to the right and left of zero indicate the positive and negative 0·1 (10%) standardised difference limits between infants treated and not treated with opioids, sedatives-hypnotics, or general anaesthetics; standardised differences of up to 10% were judged to be inconsequential. For example, the standardised difference in CRIB score between the groups treated and not treated with opioids, sedatives-hypnotics, or general anaesthetics before matching was nearly 0·5 (50%), whereas the corresponding standardised difference in the propensity-score matched pairs was 0·1 (10%). CRIB=Clinical Risk Index for Babies.

was attributable to increased CRIB scores and bedside pain assessments, whereas very preterm birth (<33 weeks of gestation), younger age (<7 h), and being already intubated at NICU admission diminished use of O-SH-GA (table 3).

In the univariate analysis, TV in neonates treated or not treated with O-SH-GA lasted for a mean of 136·2 h (SD 173·1) and 39·8 h (94·7), respectively (p<0·0001; table 5). A multivariable linear regression model adjusted for country, age at admission, sex, gestational age, intubation status at admission, CRIB and Apgar scores, intrauterine growth retardation, respiratory distress syndrome, and bedside pain assessments showed that use of O-SH-GA was still associated with an increased duration of TV (table 5).

Using the variables in table 3, propensity scores were calculated for 2004 (94%), including 1559 (78%) who were given O-SH-GA and 445 (22%) who were not, of 2142 infants in the TV group. Propensity score matching yielded 427 pairs of infants who were or were not given O-SH-GA and eliminated previous differences in covariates (figure 3 and appendix), but showed substantial increases in the duration of TV associated with the use of O-SH-GA (mean 149·0 h [SD 183·6] *vs* 38·2 h [88·5]; median 77·3 h [IQR 25·5–169·8; range 0·5–669·0] *vs* 12·5 h [5·8–28·9; 0·1–658·4]; p<0·0001). In the propensity score quintiles, use of O-SH-GA was associated with significantly increased duration of TV within each stratum (appendix). Two additional multivariable linear regression models (one including propensity score and O-SH-GA treatment status as independent variables and another including these variables plus all variables associated with duration of TV in the univariate analyses) also showed that the use of O-SH-GA was associated with increased duration of TV (data not shown). Furthermore, because in practice the use of these drugs might be a consequence of long TV, we identified neonates in the 427 matched pairs in whom the start of continuous infusion of O-SH-GA was within 6 h of the start of TV. We found 228 such pairs and again although the differences were not significant in baseline and clinical characteristics between the groups with and without O-SH-GA treatment, the duration of TV was longer in neonates who were given these drugs than in those not given the drugs. In the 228 matched pairs of neonates, the mean duration of TV for those given and not given O-SH-GA was 128·1 h (SD 162·4) and 40·1 h (93·9), respectively. These results were consistent with the inverse approach analysis with the number of ventilator-free days. In the 427 matched pairs, the median number of ventilation-free days for neonates treated with and without O-SH-GA was 22 days (IQR 9–26) and 26 days (25–27), respectively (p<0·0001).

Discussion

In our study, 34% of admissions to NICUs and 82% of neonates who were tracheally ventilated were given some sedation or analgesia (table 1). In the TV group, 74% of neonates were given opioids and a quarter were given midazolam, although wide variations existed between centres and countries in the frequency and type of neonatal sedation or analgesia (figure 1; appendix). The use of sedation or analgesia varied from 0% to 100% between centres. Our study cohort was representative of NICU populations in Europe with the participation of 18 European countries, and probably of other developed countries, uniformity of data gathering, and more than 90% inclusion rates in 16 countries.

Sedation or analgesia practices in the NICU population were previously documented in two declarative national surveys[15,16] and one cross-sectional survey.[17] Swedish NICUs reported using pharmacological analgesia during mechanical ventilation but not information about the type or frequency of drugs used;[15] 33 (37%) of 90 Italian NICUs reported routine use of opioids for mechanical ventilation.[16] The results of a survey done in 1993–94 in 14 Canadian NICUs showed that 51 (21%) of 239 neonates received analgesia or anaesthesia, or both, during 1 week.[17] In a prospective study of 217 patients (aged >28 days to 18 years) given neuromuscular blockers in PICUs, 70% were given sedatives and 72% opioids.[18] In another prospective study, 338 critically ill children were treated with 24 different sedatives and analgesics in 20 PICUs in the

UK;[19] the study population included 39 neonates and 90% of these were given morphine and 36% midazolam. In adults, according to a review of 20 surveys,[20] reported from 1999 to 2009, only two surveys were prospective—one was a national survey[21] designed to study sedation and analgesia in ventilated adults and another was an international survey[22] designed to study mechanical ventilation but not analgesia and sedation. From 2010 to 2015, we found 15 surveys, including only two national prospective studies, one from Canada[23] and another from Chile,[24] of sedation and analgesia practices in ICUs for adults. One study[25] in the USA was a retrospective assessment of a single-centre cohort and the other 12 studies (appendix) used declarative questionnaires mainly about the use of written local procedures, sedation, analgesia, sedation scales, and the routes of drug administration. Overall, very little was known about actual practice of sedation analgesia use in NICUs before this study. Also very little is known about these practices in the ICUs for adults and in PICUs.

In view of the knowledge gained over the past 30 years that neonates can feel pain[1] and evidence that all neonates have a consciousness,[26] a humane approach that includes prevention or treatment of pain in neonates is an ethical obligation.[27] This approach is further substantiated by associations between increased pain exposure and adverse developmental outcomes.[5,28,29] Although guidelines for procedural pain management in neonates exist,[30,31] there are none for prolonged sedation and analgesia in the NICU, perhaps explaining the differences in clinical practices.

In our study, 26% of all neonates and 74% of neonates in the TV group were given opioids (table 1). 60% of neonates in the TV group were given continuous infusions of O-SH-GA. Although, we did not record the exact reasons for administration of these drugs, continuous infusions were likely given with the purpose of providing sedation or analgesia during TV. Surgery, which was a potential reason for the use of O-SH-GA, was reported in only 5% of neonates in the TV group. Although this percentage seems low, it is likely that many NICUs did not have a neonatal surgical team in the same hospital and thus transferred neonates to surgical units in other hospitals. We did not gather information on this organisational aspect. Also likely is that O-SH-GA administered exclusively as boluses was given mainly for invasive procedures and less for sedation and analgesia during TV; only 4% and 1% of neonates in the TV group were given at least four boluses and at least ten boluses, respectively. Notably, 63% of neonates of all gestational ages and 71% of those younger than 33 weeks of gestation in the TV group were already intubated at admission to the NICU. This finding is consistent with tracheal intubation being both a marker of illness severity and a common reason for admission to the NICU. With the high rate of infants born in the same hospital as the NICU, most of these tracheal intubations were likely done in the delivery room. Since we did not gather data on medications used before admission to the NICU, we did not record whether any sedation or analgesia was used for tracheal intubation, any other procedure, or mechanical ventilation before admission to the NICU. Although this information would have been useful, the aim in our study was to ascertain sedation and analgesia practices in the NICU; furthermore, we felt that the gathering of data by staff who did not participate in the study reduced the reliability of the data. We do not know whether the medications that were used for sedation and analgesia in neonates before admission to the NICU had any effects on our results, particularly for neonates intubated before admission. Nonetheless, the propensity score matching was used with the aim of minimising bias created by baseline characteristics. Discussion about opioid use in ventilated neonates include developmentally regulated pain sensitivity, clinical instability from acute pain or stress, unsynchronised breathing, and suboptimum ventilation,[32] and long-term effects on brain development.[33–36] A Cochrane review concluded that opioids reduce neonatal pain scores, and do not prolong ventilation, alter mortality or subsequent intelligence, motor function, or behaviour,[33] but evidence for the routine treatment of ventilated newborn babies with opioids is insufficient. Variations exist in the patterns of opioid use in European countries. Sufentanil, for example, was used mostly in France and Poland, despite sparse data on its use.[37] Another review concluded that remifentanil and fentanyl are more effective than is morphine for tracheal intubation.[38] About a quarter of neonates who had TV in this study did not receive any opioids. This might be explained, partly, by the use of morphine neither improving neonatal neurodevelopmental outcomes[39] nor providing adequate analgesia for procedural pain in preterm neonates given TV.[40] Health providers also fear that opioid use could prolong the length of TV. Nonetheless, we should keep in mind that alleviation of neonatal pain and suffering is a sufficient reason to use adequate analgesics, including opioids, in this population. In this study, the analysis of matched pairs showed that 25% of tracheally ventilated neonates who were not given O-SH-GA were ventilated for more than 28·9 h and one neonate for at least 658·4 h. Overall, midazolam was by far the most common sedative used. It was given to 25% of neonates who had TV and its use varied from 0% to 73% between European countries (appendix), despite few clinical data to lend support for midazolam sedation for neonates.[41,42] Dexmedetomidine, which is frequently used for sedation of adults in the ICU, was not used in our study. The results of a phase 2–3 study have shown that dexmedetomidine is effective for sedating preterm and full-term neonates and is well tolerated without substantial adverse effects;[43] preterm neonates had reduced plasma clearance and increased elimination half-life.

Consistent with the results of previous studies, logistic regression analyses showed independent associations of sedation and analgesia with ventilation status, pain assessment,[44] and severity of illness.[45] Contrary to the results of a 2010 systematic review and meta-analysis[33] that opioid exposure did not have an effect on the duration of TV in the neonate, in our study exposure to O-SH-GA was associated with prolonged ventilation in the neonates. Additional multivariable analyses (propensity score matching, stratification, and regression adjustment) and analyses in infants in whom these medications were started early after initiation of TV substantiated this finding, consistent with the findings from randomised trials of drug-related respiratory depression in neonates.[45–47] Propensity score matching allowed the elimination of differences in baseline characteristics between infants who received O-SH-GA and those who did not. Potential confounders such as being on TV at NICU admission were balanced with this approach. Before matching, 59% of infants who were given O-SH-GA and 80% who were not given O-SH-GA were already intubated at admission ($p<0·0001$; appendix); after matching, these frequencies were 77% and 79% ($p=0·325$; appendix). Illness severity, as assessed with the CRIB score, was not different after matching (appendix). Also, because the use of O-SH-GA could be a consequence of prolonged TV and not its cause, we confirmed our findings in a subgroup of matched pairs in whom the start of continuous infusion of these drugs was within 6 h of the initiation of TV. Neonatal brains are deficient in P-glycoprotein, which is needed for active extrusion of sedatives and analgesics from the brain,[48] thus increasing their respiratory depressant effects. Delayed excretion of these drugs, particularly in preterm neonates,[49] might also lead to respiratory depression. Furthermore, after initiating O-SH-GA in tracheally ventilated neonates, some clinicians might not discontinue this treatment until the newborn baby is ready for extubation or is extubated.[50] 25% of neonates in the TV group were given O-SH-GA for more than 5–7 days (appendix), increasing the risk of tolerance, withdrawal syndromes, and iatrogenic injury.[51] Little information exists about other drug classes, although their effects on neonatal respiratory drive might be similar to opioids. Use of non-pharmacological treatments or analgesics without respiratory depressant effects for pain or stress could avoid respiratory depression in neonates.[52]

The frequencies of pain assessments were 58%, 45%, and 30% in the TV, NIV, and SV groups, respectively (table 1). These data are worrying because pain assessment should be standard of care in all neonates. Surprisingly, units that administered O-SH-GA often did not do accompanying pain assessments. However, neonatal pain assessment is not an easy task and the existence of several scales can be confusing.[53] More research is needed on the implementation of pain scales at the bedside and on the ways of optimising pain management with pain assessments in neonates. Opioids or benzodiazepines were weaned gradually in 39%, 31%, and 42% of neonates in the TV, NIV, and SV groups, respectively. This practice is consistent with current recommendations. According to the American Academy of Pediatrics (AAP), each clinical unit should establish a threshold of cumulative exposure to opioids and benzodiazepines above which drug dependency can be expected to occur with a likelihood that justifies anticipatory initiation of a weaning protocol. For example, setting a threshold at a cumulative fentanyl exposure of more than 2 mg/kg or for longer than 7 days would predict a likelihood of dependency of more than 50% but less than 100%.[54] Infants with a cumulative exposure to opioids or benzodiazepines below the thresholds for initiation of weaning protocols can have a rapid taper of these medications over 24–48 h; those above the thresholds might need longer weaning of up to 2–3 weeks.[54] The AAP also recommends that signs of drug withdrawal be scored with a validated abstinence assessment scale. Infants with confirmed drug exposure who are unaffected or showing minimum signs of withdrawal do not need medications. Although different medications were used to treat or prevent drug withdrawal syndromes in this study, morphine was used most commonly. The little available evidence from controlled trials of neonatal opioid withdrawal lends support for the use of oral morphine solution and methadone when pharmacological treatment is indicated; increasing evidence suggests that oral clonidine is also effective either as a primary or adjunctive treatment, but further prospective trials are warranted.[54]

Interpretation of our results must be tempered by the limitations. First, the participation of eligible units varied widely between countries and might not represent each country's practices. In most countries, however, several large NICUs providing advanced neonatal intensive care participated and allowed us to sample a mean of about 0·15% births (appendix). Second, we cannot exclude a Hawthorne effect (ie, a reaction in which individuals modify or improve their behaviour in response to their awareness of being observed), with altered bedside practices during study enrolment. However, data gathering for 24 h per day for 28 days might have minimised this tendency. Third, as a trade-off between study design and protocol compliance, we did not record the doses of medications used for sedation and analgesia in neonates. Requiring these data would have created massive burdens on the NICU staff, lowering our participation rate in each country, or protocol compliance within each NICU, or increasing the rates of missing or incomplete data. For the same reasons, we did not record the purposes for the use of sedation and analgesia. Thus, we did not record how often these medications were used for

mechanical ventilation or for invasive procedures. The epidemiology of invasive procedures in the NICU has already been reported.[55] Fourth, our models of the factors associated with the use of sedation and analgesia might be subject to bias because neonates were classified on the basis of ever or never use of sedation and analgesia. This dichotomy gives neonates who were given occasional sedation and analgesia the same weighting as those who were given frequent and longlasting sedation and analgesia. Last, we cannot exclude a potential bias in the association noted between the use of O-SH-GA and longer duration of tracheal ventilation using the propensity score approach. Although propensity score techniques can balance baseline covariates between exposure groups, they cannot balance unmeasured characteristics or unknown confounders. We could postulate that illness severity, not measured by the CRIB score, remains a potential confounder. Thus, as with all observational studies, propensity score analyses have the limitation that remaining unmeasured confounding might still be present.

Our findings emphasise the need to develop international guidelines for the judicious use of sedation and analgesia in the NICU, to investigate the therapeutic and adverse effects of these drugs in neonates, and to develop new, safe approaches for sedation and analgesia in neonates.

Contributors

RC, ME, and KJSA were responsible for the study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, obtaining funding, and study supervision. EC was responsible for the acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, and study supervision. LB and HL were responsible for obtaining funding, interpretation of data, and critical revision of the manuscript for important intellectual content. EB, AA-A, RDA, KS, TPo, CM, PL, TPa, SAM, M-LI, SS, RT, BvO, AB, AD, and MS were responsible for acquisition of data and critical revision of the manuscript for important intellectual content.

Declaration of interests

We declare no competing interests.

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